Patient Heterogeneity in Health Economic Decision Models for Chronic Obstructive Pulmonary Disease

Hoogendoorn, Martine; Feenstra, Talitha L; Asukai, Yumi; Briggs, Andrew H; Borg, Sixten; Dal Negro, Roberto W; Hansen, Ryan N; Jansson, Sven-Arne; Leidl, Reiner; Risebrough, Nancy

Published in:
Value in Health

DOI:
10.1016/j.jval.2016.04.002

VALUE IN HEALTH 19 (2016) 800–810

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

ECONOMIC EVALUATION

Patient Heterogeneity in Health Economic Decision Models for Chronic Obstructive Pulmonary Disease: Are Current Models Suitable to Evaluate Personalized Medicine?

Martine Hoogendoorn, PhD[1,], Talitha L. Feenstra, PhD[2,3], Yumi Asukai, MSc[4], Andrew H. Briggs, DPhil[5], Sixten Borg, MSc[6,7,8], Roberto W. Dal Negro, MD, PhD[9], Ryan N. Hansen, PharmD, PhD[10], Sven-Arne Jansson, PhD[11], Reiner Leidl, PhD[12], Nancy Risebrough, PhD[13], Yevgeniy Samyshkin, MSc[4], Margarethe E. Wacker, MSc[12], Maureen P.M.H. Rutten-van Mölken, PhD[1]*

[1]*Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands;* [2]*Department for Prevention and Health Services Research, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands;* [3]*Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands;* [4]*IMS Health, Health Economics and Outcomes Research and Real-World Evidence Solutions, London, UK;* [5]*Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK;* [6]*The Swedish Institute for Health Economics, Lund, Sweden;* [7]*Health Economics Unit, Department of Clinical Sciences in Malmö, Lund University, Lund, Sweden;* [8]*Evidera, London, UK;* [9]*National Center for Respiratory Pharmacoeconomics and Pharmacoepidemiology (CESFAR), Verona, Italy;* [10]*Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy, University of Washington, Seattle, WA, USA;* [11]*Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine, The OLIN Unit, Umeå University, Umeå, Sweden;* [12]*Helmholtz Zentrum München, Institute of Health Economics and Health Care Management, Member of the German Center for Lung Research, Comprehensive Pneumology Center Munich, Neuherberg, Germany;* [13]*ICON Health Economics, Toronto, Ontario, Canada*

ABSTRACT

Objectives: To assess how suitable current chronic obstructive pulmonary disease (COPD) cost-effectiveness models are to evaluate personalized treatment options for COPD by exploring the type of heterogeneity included in current models and by validating outcomes for subgroups of patients. **Methods:** A consortium of COPD modeling groups completed three tasks. First, they reported all patient characteristics included in the model and provided the level of detail in which the input parameters were specified. Second, groups simulated disease progression, mortality, quality-adjusted life-years (QALYs), and costs for hypothetical subgroups of patients that differed in terms of sex, age, smoking status, and lung function (forced expiratory volume in 1 second [FEV_1] % predicted). Finally, model outcomes for exacerbations and mortality for subgroups of patients were validated against published subgroup results of two large COPD trials. **Results:** Nine COPD modeling groups participated. Most models included sex (seven), age (nine), smoking status (six), and FEV_1% predicted (nine), mainly to specify disease progression and mortality. Trial results showed higher exacerbation rates for women (found in one model), higher mortality rates for men (two models), lower mortality for younger patients (four models), and higher exacerbation and mortality rates in patients with severe COPD (four models). **Conclusions:** Most currently available COPD cost-effectiveness models are able to evaluate the cost-effectiveness of personalized treatment on the basis of sex, age, smoking, and FEV_1% predicted. Treatment in COPD is, however, more likely to be personalized on the basis of clinical parameters. Two models include several clinical patient characteristics and are therefore most suitable to evaluate personalized treatment, although some important clinical parameters are still missing.
Keywords: COPD, model, patient heterogeneity, validation.

Introduction

Personalized medicine has the potential to improve the (cost-) effectiveness of treatments and contribute to health care cost containment. Hence, interest in personalized medicine has increased exponentially in the past decade [1]. The concept of personalized medicine has different definitions [2,3]. Some definitions focus on the use of genetics, proteomic, cytomic, and/or metabolic biomarkers to define patient genotypes and phenotypes most likely to benefit most from a certain treatment. Other definitions are broader and refer to customizing treatment to the individual characteristics, needs, and preferences of a patient

* *Address correspondence to:* Martine Hoogendoorn, Institute for Medical Technology Assessment, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

E-mail: hoogendoorn@imta.eur.nl.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2016.04.002

during all stages of care, including prevention, diagnosis, treatment, and follow-up [3]. The expectations of personalized medicine are high, but so far, the cost-effectiveness of such technologies on average has not been found to be any better than that of nonpersonalized interventions [4,5]. Thus, economic evaluation studies are needed to show whether the personalized approach indeed leads to greater efficiency in health care compared with the one-size-fits-all approach.

If based on health economic models, such economic evaluations of personalized treatment strategies based on demographic and clinical patient characteristics require models that are able to address the heterogeneity due to those patient characteristics appropriately. However, most currently available cost-effectiveness models are cohort Markov or state-transition models that have only limited capability for addressing patient heterogeneity. Most published cost-effectiveness analyses similarly focused on results for the average patient. Current guidelines for health economic modeling recognize the importance of patient heterogeneity, but there is a lack of consensus on how to best address this in a modeling framework [6].

One of the major chronic diseases for which treatment is increasingly personalized is chronic obstructive pulmonary disease (COPD). In 2011, the new Global Initiative for chronic Obstructive Lung Disease guidelines proposed a new classification system for patients with COPD based on lung function, symptoms, and exacerbations. Although this new classification is a step forward to personalized treatment for COPD, proposed treatment guidelines for the subgroups of patients still need to be validated [7]. Manufacturers of drugs and devices are increasingly focused on specific phenotypes of patients, such as patients with frequent exacerbations, a rapid decline in lung function, persistent systemic inflammation, raised eosinophil concentrations, and bacterial colonization [8,9]. In addition, caregivers providing multidisciplinary integrated care programs develop different treatment modules for subgroups of patients who need physical reactivation, smoking cessation support, nutritional interventions, treatment of depression, and so forth. In contrast, most decisions about the reimbursement of new treatments are still made for large groups of patients and on the basis of evaluations that do not consider patient heterogeneity. This is expected to change rapidly because biologics for COPD are under development [10] and payers are likely to limit the reimbursement of these expensive drugs to specified subgroups. Moreover, new drugs for COPD that have recently been launched or are still under development are often quite similar to the currently marketed drugs, which makes it increasingly difficult to demonstrate their value for money unless one can specify the subgroup for which they are particularly beneficial.

In the past years, several health economic decision models for COPD have been published. In 2011, our modeling group took the initiative to establish a network of people involved in COPD modeling around the world (COPD modeling teams, pharmaceutical companies interested in COPD modeling, epidemiologists, clinicians, etc.). Up to now, we have organized three 1-day meetings in 2011, 2012, and 2014 with the aim to compare the different available models with respect to model structure and input parameters and to cross-validate the models against each other [11]. Proceedings of the third meeting regarding patient heterogeneity are described in the present article.

The aim of this article was to assess how suitable current models are to evaluate the cost-effectiveness of personalized treatment options for COPD. First, we explored which type of patient heterogeneity is included in currently available COPD cost-effectiveness models to see whether the models are able to evaluate subgroups of patients with COPD that are considered clinically relevant. Second, we investigated the impact of patient characteristics on the outcomes. Finally, we validated the outcomes of specific subgroup analyses with the models against subgroup results of clinical trials to assess whether the models are suitable for performing subgroup analyses. These questions are relevant because most of the models are initially built to evaluate treatment options for a large group of patients with COPD.

Methods

Procedure

In March 2014, the COPD modeling groups that participated in previous meetings as well as new groups identified through publications or other participants within the network were contacted to explore their interest in participation in the third COPD modeling meeting and in running the model simulations required for this heterogeneity analysis. Modeling groups were first asked to specify which patient characteristics are currently included in their model and which input parameters are specified by subgroup. Second, they were asked to run their model for hypothetical patients who differed in terms of patient and disease characteristics to explore the impact of these characteristics on the outcomes of the models. Third, they were asked to simulate the outcomes for subgroups of patients that had similar characteristics as the subgroups of two large randomized controlled clinical trials to validate the model outcomes. Results were returned to the organizers of the meeting in a structured format in Microsoft Excel 2 weeks before the meeting. The combined results of the models were circulated to all participants of the COPD modeling meeting 1 week before the meeting to give participants time to reflect on the outcomes. The results were presented during the meeting and explanations for the differences in outcomes between the models were discussed.

Participating Models

Nine COPD models participated in the model simulations. Six of these nine models also participated in the previous meeting in 2012 [12–17]. A short description of these six models can be found in the publication about the proceedings of this second COPD modeling meeting [11]. Three new models also participated. The simulation model of Asukai et al. [18] was published in 2013. The other two models have not yet been published, but have been presented at international conferences. The model of Briggs et al. (GALAXY COPD model) was presented at the ISPOR Annual International meeting 2013 and the ISPOR 17th Annual European Congress 2014 [19,20]. The model of Dal Negro [21] was also presented at the ISPOR 17th Annual European Congress 2014 [21].

Content of the Modeling Challenge

For the first part of the modeling challenge, groups reported all patient characteristics that are currently included in their models. Furthermore, groups provided the level of detail in which the following input parameters had been specified in the models: disease progression, exacerbation frequency, mortality, case-fatality of an exacerbation, utilities during stable disease, utilities during exacerbations, maintenance costs, and exacerbation-related costs.

In part two, modeling groups simulated the outcomes for hypothetical subgroups of patients that differ in terms of sex, age, smoking status, and level of forced expiratory volume in 1 second (FEV_1) % predicted to see how patient heterogeneity affected effects and costs within one model and between models. Sex, age, smoking status, and FEV_1% predicted were chosen because these are the factors that are included in most models. In the first simulation, outcomes for a 65-year-old, ex-smoking, male patient with severe COPD were calculated. In each of the following four simulations, one of the patient characteristics was changed:

Table 1 – Baseline characteristics of subgroups within the placebo group of the UPLIFT and TORCH trials used as starting population of the model simulations [24–27].

Characteristic	UPLIFT trial					TORCH trial	
	By sex		By age	By smoking status		By COPD severity	
	Males	Females	Age < 50 y	Smokers	Ex-smokers	Moderate COPD	Severe COPD
N	2222	784	172	432	1791	535	775
Sex: males (%)	100	0	58	62	78	72	76
Age (y), mean ± SD	65 ± 8	62 ± 9	<50	61 ± 9	66 ± 9	65 ± 9	65 ± 8
Current smokers (%)	26	40	57	100	0	47	43
Postbronchodilator FEV_1% predicted, mean ± SD	47 ± 13	49 ± 13	47 ± 15	50 ± 15	46 ± 15	59 ± 7	40 ± 6
GOLD II: moderate COPD (%)	44	48	48	54	41	100	0
GOLD III: severe COPD (%)	45	43	36	38	48	0	100
GOLD IV: very severe COPD (%)	10	7	15	7	10	0	0

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; TORCH, TOwards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-Term Impacts on Function with Tiotropium.

female instead of male patient, 75-year-old instead of 65-year-old patient, smoking instead of ex-smoking patient, and patient with moderate COPD instead of severe COPD. The outcomes of each of these four simulations were compared with the results of the first simulation.

In part three, the validity of the subgroup analyses with the models was investigated by comparing the model outcomes against published subgroup results of two large randomized controlled clinical trials, the 4-year Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial and the 3-year TOwards a Revolution in COPD Health (TORCH) trial [22,23]. In the UPLIFT trial, almost 6000 patients with moderate-to-very severe COPD were randomized to placebo, defined as all regular respiratory medications except inhaled anticholinergics, or tiotropium 18 μg plus all regular respiratory medications except other inhaled anticholinergics [22]. In the TORCH trial, slightly more than 6000 patients with moderate-to-very severe COPD were randomized to placebo, defined as all COPD medications except long-acting bronchodilators and inhaled corticosteroids, salmeterol 50 μg, fluticasone 500 μg, or the combination of salmeterol 50 μg and fluticasone 500 μg [23]. For both the UPLIFT trial and the TORCH trial, several subgroup analyses have been published mainly by sex, age, smoking status, and level of FEV_1% predicted [24–27]. The modeling groups were asked to adjust the starting population of the model to the baseline characteristics of the specific subgroups within the placebo group of the trial in terms of percentage of males, mean age, percentage of current smokers, and mean FEV_1% predicted (or distribution over the GOLD severity stages moderate, severe, or very severe COPD). The baseline characteristics of the subgroups in the trial are presented in Table 1. For comparison with the UPLIFT trial placebo arm, groups were asked to run the simulations assuming that patients received all regular respiratory medications except inhaled anticholinergics. Simulation of the TORCH trial placebo arm was done assuming that patients did not use long-acting bronchodilators and inhaled corticosteroids.

Outcomes

For part two of the challenge, the following outcomes were reported: disease progression defined as decline in lung function, mortality, quality-adjusted life-years (QALYs) per patient, and total costs per patient. These outcomes were calculated for both 1-year and lifetime horizons. For part three of the challenge, the total number of exacerbations per patient-year and all-cause mortality was calculated including the uncertainty around the outcomes if possible. The time horizon of the model simulations was similar to the duration of the clinical trials: 3 years for the TORCH trial and 4 years for the UPLIFT trial.

Results

Table 2 presents the patient characteristics included in the nine participating cost-effectiveness models. Most models include sex, age, smoking status, and FEV_1% predicted. Newer models also included patient characteristics such as previous exacerbations, body mass index (BMI), and comorbidities (Asukai_simulation model and Briggs). Table 3 presents the level of specification for the most important input parameters. The level of detail in which the input parameters are specified varies greatly between the models. Table 4 presents the results for the model simulations of hypothetical patients who differ in terms of sex, age, smoking status, and FEV_1% predicted. The validation of subgroup analysis in the models against the outcomes of the subgroup analyses in the clinical trials is presented in Figures 1 to 4. In subsequent sections, the results will be discussed separately for the four patient characteristics that most of the models have in common: sex, age, smoking status, and FEV_1% predicted. For each characteristic we first present the results for the simulations of hypothetical patients followed by the simulations of the subgroups in the clinical trials.

Sex

Seven models included sex as patient characteristic (Asukai_Markov, Asukai_simulation, Briggs, Dal Negro, Hoogendoorn, Samyshkin, and Wacker). Sex was mainly included to specify disease progression (six models) and mortality (six models) (Asukai_Markov, Asukai_simulation, Briggs, Dal Negro, Hoogendoorn, and Samyshkin) (Table 3). Results of the comparison of hypothetical subgroups of patients showed, however, that three of the models that included sex reported a disease progression rate that was similar for men and women (Asukai_Markov, Dal Negro, and Hoogendoorn) (Table 4), whereas three models had faster disease progression rates for women (Asukai_simulation, Briggs, and Samyshkin). Five models had a higher 1-year mortality rate for male patients than for female patients (Asukai_Markov, Asukai_simulation, Brigs, Hoogendoorn, and

Table 2 – Patient characteristics included in nine COPD cost-effectiveness models.

Characteristic	Asukai_Markov model	Asukai_simulation model	Borg	Briggs	Dal Negro	Hansen	Hoogendoorn	Samyshkin	Wacker
Sex	X	X		X	X		X	X	X
Age	X	X	X	X	X	X	X	X	X
Smoking	X	X		X		X	X		X
FEV_1 % predicted	X	X	X	X	X	X	X	X	X
Height		X							
Previous exacerbations		X	X	X					
BMI		X		X					
Comorbidities		X		X	X				
No. of ER visits/hospitalizations		X							
Rapid decline in FEV_1			X		X				
Dyspnea (mMRC)				X					
Disease-specific quality of life (SGRQ)				X					
Utility (EQ-5D)				X					
Activity (6 MWD)				X					
Residual volume					X				
DLCO					X				
Lung transplantation									X

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DLCO, diffusion lung capacity for carbon monoxide; ER, emergency room; EQ-5D, EuroQol five-dimensional questionnaire; FEV_1, forced expiratory volume in 1 s; mMRC, modified Medical Research Council dysnpnea scale; RV, residual volume; 6MWD, six-minute walking distance; SGRQ, St. George's Respiratory Questionnaire.

Table 3 – Level of specification of important input parameters.

Model	Type of input parameter						
	Disease progression specified by	Exacerbation frequency specified by	Mortality specified by	Utilities during stable disease specified by	Utilities during exacerbations specified by	Maintenance costs specified by	Exacerbation-related costs specified by
Asukai_Markov model	Sex, age, smoking (indirectly)	FEV_1% pred.	Sex, age, FEV_1% pred.	FEV_1% pred.	Exacerbation severity	FEV_1% pred.	Exacerbation severity
Asukai_simulation model	Sex, age, smoking, FEV_1% pred.	FEV_1% pred.	Sex, age, FEV_1% pred.	Sex, age, FEV_1%pred., BMI, comorbidities, no. or ER visits/ hospitalizations	Exacerbation severity	FEV_1% pred.	Exacerbation severity
Borg	Age, FEV_1% pred., rapid decline	FEV_1% pred., frequent exacerbations	Age, FEV_1% pred.	FEV_1% pred.	Exacerbation severity, FEV_1% pred*	FEV_1% pred.	Exacerbation severity
Briggs	Sex, age, smoking, FEV_1% pred. + all other listed in Table 2	Sex, age, smoking, FEV_1% pred. + all other listed in Table 2	Sex, age, smoking, FEV_1% pred. + all other listed in Table 2	Sex, age, smoking, FEV_1% pred. + all other listed in Table 2	Sex, age, smoking, FEV_1% pred. + all other listed in Table 2	Sex, age, smoking, FEV_1% pred. + all other listed in Table 2	Sex, age, smoking, FEV_1% pred. + all other listed in Table 2
Dal Negro	Sex, age, RV, DLCO, BODE, % FEV decline, comorbidities	Age, RV, DLCO, BODE, % FEV decline, comorbidities	Age, RV, DLCO, BODE, % FEV decline, comorbidities	Age, RV, DLCO, BODE, % FEV decline, comorbidities	Age, FEV_1% pred., RV, DLCO, BODE, % FEV decline, comorbidities	Age, FEV_1% pred., RV, DLCO, BODE, % FEV decline, comorbidities	Age, FEV_1% pred., RV, DLCO, BODE, % FEV decline, comorbidities
Hansen	Smoking, FEV_1% pred.	FEV_1% pred.	Age, FEV_1% pred.	FEV_1% pred.	FEV_1% pred.	FEV_1% pred.	FEV_1% pred.
Hoogendoorn	Sex, age, smoking, FEV_1% pred.	FEV_1% pred.	Sex, age, smoking, FEV_1% pred.	FEV_1% pred.	Exacerbation severity	Sex, age, FEV_1% pred.	Exacerbation severity
Samyshkin	Sex, age, FEV_1% pred.	FEV_1% pred.	Sex, age, FEV_1% pred.	FEV_1% pred.	Exacerbation severity	FEV_1% pred.	Exacerbation severity
Wacker	Smoking, FEV_1% pred.	FEV_1% pred, lung transplant	Sex, age, smoking, FEV_1% pred., lung transplant	FEV_1% pred., lung transplant	FEV_1% pred., exacerbation severity, lung transplant	Age, FEV_1% pred., lung transplant	Age, FEV_1% pred., exacerbation severity, lung transplant

BODE, Body-mass index, airflow Obstruction, Dyspnea and Exercise index; DLCO, diffusion lung capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; pred., predicted; RV, residual volume.

* A disutility that depends on exacerbation severity is applied to the utility of stable disease.

Table 4 – One-year model outcomes for a hypothetical reference patient (analysis 1) and for patients who differ on one patient characteristic compared with the reference patient (analyses 2–5).

Analysis	Model								
	Asukai_Markov	Asukai_simulation	Borg*	Briggs	Dal Negro	Hansen	Hoogendoorn	Samyshkin	Wacker
1. Male patient, 65 y, ex-smoking with severe COPD (=comparator)									
Disease progression (%)†	12.8	0.4	5.5	–0.51 pred.	10.0	5.2	2.8	11.9	2.5
Mortality (%)	4.0	4.7	7.2	2.8	10.0	3.1	7.1	4.9	12.4
QALYs	0.752	0.627	0.688	0.581	NA	0.658	0.723	0.724	0.520
Costs (2014 $)	1950	1560	2350	3830	2680–4020	2260	1680	2270	2480
2. *Female* patient, 65 y, ex-smoking with severe COPD									
Disease progression (%)†	12.8	0.9	‡	–0.81% pred.	10.0	‡	2.8	16.7	2.5
Mortality (%)	3.6	3.3	‡	2.6	10.0	‡	4.7	4.9	7.9
QALYs	0.754	0.406	‡	0.623	NA	‡	0.723	0.721	0.530
Costs (2014 $)	1950	1590	‡	3090	2680–4020	‡	2050	2320	2540
3. Male patient, 75 y, ex-smoking with severe COPD									
Disease progression (%)†	11.4	0.5	5.6	–0.57 pred.	20.0	5.2	3.6	11.6	2.1
Mortality (%)	6.1	13.8	24.1	5.5	20.0	9.3	13.2	12.2	27.2
QALYs	0.742	0.598	0.624	0.593	NA	0.643	0.723	0.696	0.470
Costs (2014 $)	1900	1460	2090	4010	4020–5360	2200	2090	2180	2290
4. Male patient, 65 y, *smoking* with severe COPD									
Disease progression (%)†	12.8	2.3	‡	–1.27% pred.	‡	8.6	3.6	‡	7.6
Mortality (%)	4.0	4.8	‡	3.6	‡	3.1	8.1	‡	17.7
QALYs	0.752	0.627	‡	0.548	‡	0.657	0.723	‡	0.500
Costs (2014 $)	1950	1600	‡	3840	‡	2270	1680	‡	2450
5. Male patient, 65 y, smoking with *moderate COPD*§									
Mortality (%)	2.5	3.3	5.3	1.7	8.0	2.5	5.0	3.0	6.3
QALYs	0.781	0.653	0.741	0.623	NA	0.702	0.737	0.772	0.570
Costs (2014 $)	330	450	1060	3910	2010–2680	1580	1270	1540	1460

COPD, chronic obstructive pulmonary disease; NA, not available for this model; pred., predicted; QALY, quality-adjusted life-year.

* The runs from this model reflect a prevalent mix of 52% male patients and 48% female patients, of which 41% are current smokers.

† *Disease progression* was defined as the percentage of patients with severe COPD moving to very severe COPD except for the model of Briggs et al. in which disease progression was defined as the decline in FEV_1% predicted.

‡ Subgroup analysis not possible for this model.

§ For this subgroup, disease progression is not a relevant outcome because the percentage of patients with moderate COPD moving to severe COPD is not comparable with the first subgroup analysis that serves as comparator.

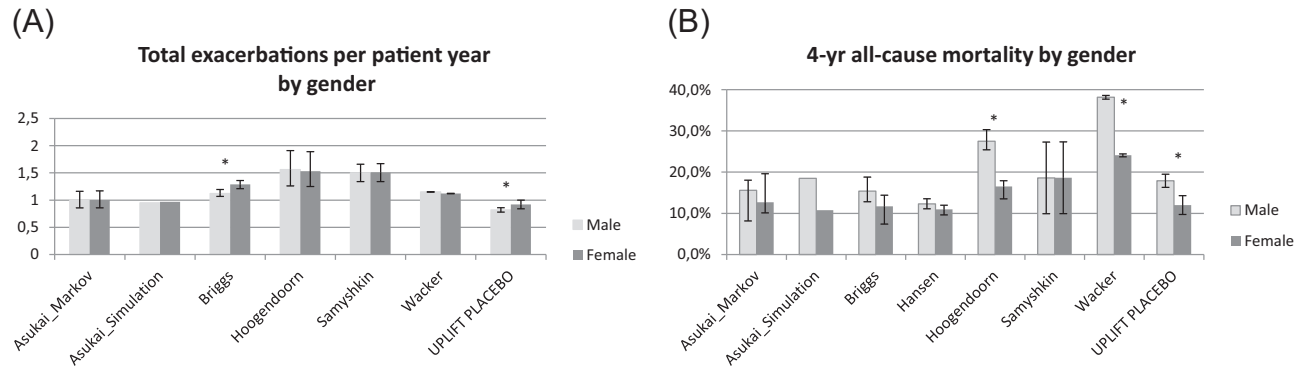

Fig. 1 – Comparison of model results for the subgroup sex with empirical results of the 4-year UPLIFT trial for (A) exacerbations and (B) all-cause mortality. *Difference is statistically significant. Difference in the simulation model of Asukai could not be tested because no uncertainty was available around the estimates. UPLIFT, Understanding Potential Long-Term Impacts on Function with Tiotropium.

Wacker), whereas in one model mortality rate in men and women was comparable (Samyshkin). A few models specified utilities during stable disease and/or COPD-related maintenance costs by sex (Table 3) (Asukai_simulation, Briggs, and Hoogendoorn). The simulation model of Asukai et al. specifying utility weights by sex reported a lower number of QALYs for a female patient than for a male patient, despite a lower female mortality, whereas the model of Briggs et al. had a slightly higher number of QALYs for female patients. Of the two models specifying maintenance costs by sex, one used higher costs for women (Hoogendoorn), whereas the other model (Briggs) included lower costs for women than for men. Validation of the model results with respect to sex against empirical data showed that in the UPLIFT study male patients had fewer exacerbations (rate ratio [RR] = 0.89; 95% confidence interval [CI] 0.81–0.98) compared with female patients, whereas this was found only in the model of Briggs (Fig. 1A). The other models reported equal rates for women and men. Four-year all-cause mortality in the UPLIFT trial was reported to be higher for men (RR = 1.49; 95% CI 1.21–1.84)), which was found in two models (Hoogendoorn and Wacker) (Fig. 1B).

Age

All nine participating models included age as characteristic mainly to specify disease progression (seven models) and mortality (nine models). In one model, disease progression was lower for a 75-year-old patient than for a 65-year-old patient (Asukai_Markov). In the models of Dal Negro and Hoogendoorn, disease progression increased with increasing age, whereas in the remaining models disease progression was about equal for both ages (Table 4). In all models, 1-year mortality was higher for a 75-year-old patient than for a 65-year-old patient (1.5-3.3 times higher). Only one model reported higher QALYs for an older patient (Briggs). Three of the four models that specified costs by age (Briggs, Dal Negro, Hoogendoorn, and Wacker) reported higher costs for an older patient (Briggs, Dal Negro, and Hoogendoorn). Validation of the model results with respect to age against the outcomes of the UPLIFT study showed that in all models except one, the exacerbation rate in the subgroup of patients younger than 50 years was equal to the exacerbation rate in the total population (mean age 65 years), which was in accordance with the trial results (Fig. 2A). Only in the model of Briggs, the subgroup of patients younger than 50 years had a significantly lower exacerbation rate than did the total population. In the subgroup of younger patients in the UPLIFT study, 4-year all-cause mortality was significantly lower compared with that of the total population (RR = 0.43; 95% CI 0.25–0.74), which was also found in four models (Briggs, Hansen, Hoogendoorn, and Wacker) (Fig. 2B).

Smoking Status

Six of the nine models included smoking status as patient characteristic (Asukai_Markov, Asukai_simulation, Briggs, Hansen, Hoogendoorn, and Wacker). In all six models, disease progression was specified by smoking status (Table 3) as smokers

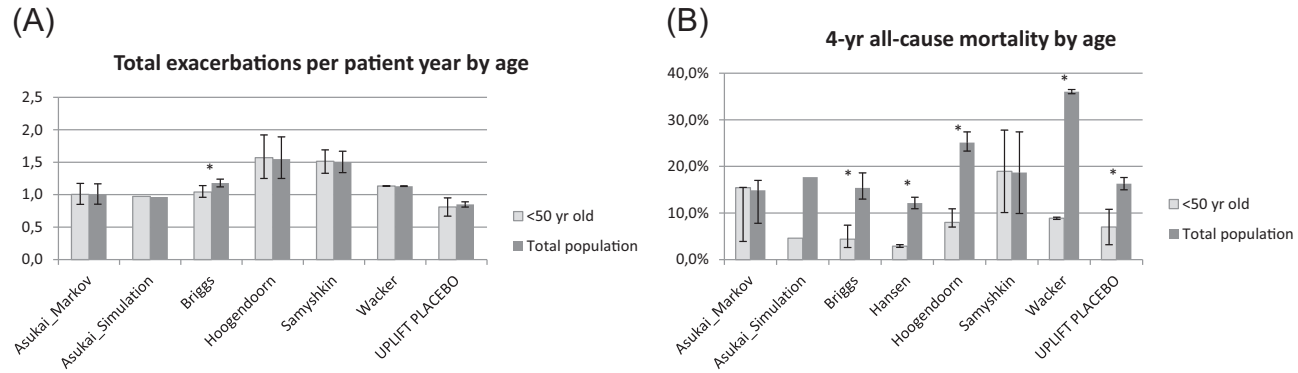

Fig. 2 – Comparison of model results for the subgroup age with empirical results of the 4-year UPLIFT trial for (A) exacerbations and (B) all-cause mortality. *Difference is statistically significant. Difference in the simulation model of Asukai could not be tested because no uncertainty was available around the estimates. UPLIFT, Understanding Potential Long-Term Impacts on Function with Tiotropium.

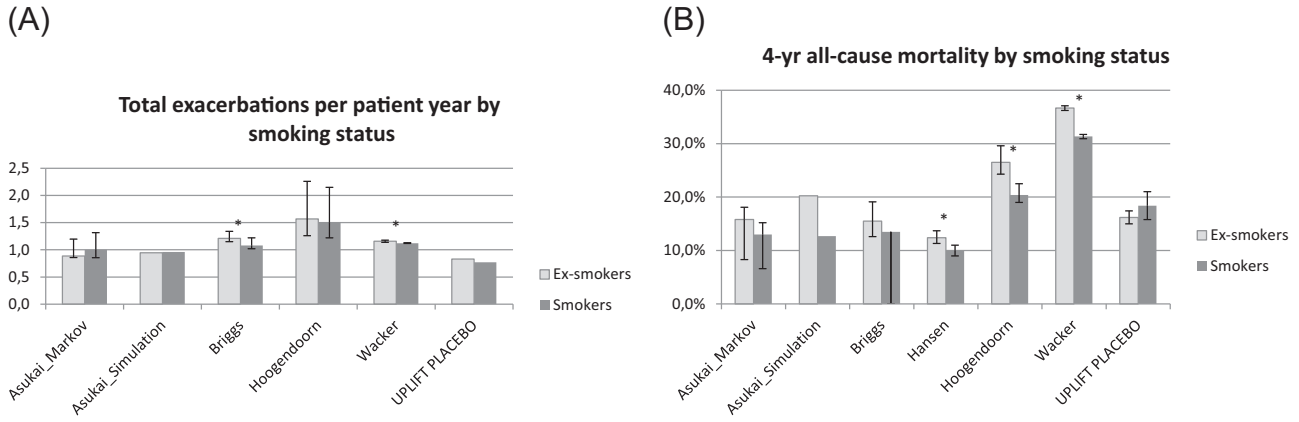

Fig. 3 – Comparison of model results for the subgroup smoking status with empirical results of the 4-year UPLIFT trial for (A) exacerbations and (B) all-cause mortality. *Difference is statistically significant. Difference in the simulation model of Asukai and the trial (exacerbations) could not be tested because no uncertainty was available around the estimates. Uplift, Understanding Potential Long-Term Impacts on Function with Tiotropium.

having a higher disease progression compared with ex-smokers (Table 4). Three models specified mortality by smoking status (Briggs, Hoogendoorn, and Wacker). One-year mortality in these models was higher for smokers (Table 4). Only in the model of Briggs et al., smoking status was modeled to have an association with other input parameters such as utilities and costs (Table 3). As a result, the 1-year QALYs and costs were (almost) equal for a patient who smoked compared with an ex-smoking patient in the models (Table 4). The UPLIFT study showed no difference in exacerbations between smokers and ex-smokers, which was in line with the results of most models, except for two (Briggs and Wacker) that reported a higher exacerbation rate for ex-smokers. Four-year mortality in the UPLIFT trial was also not found to be different between smokers and ex-smokers. Three models, however, reported a significantly higher mortality rate for ex-smokers than for smokers (Hansen, Hoogendoorn, and Wacker), most likely because ex-smokers in the UPLIFT trial were older than the smokers and not because of their difference in smoking status. This is confirmed by Table 4, which isolates the impact of smoking status from the impact of age.

FEV_1% predicted

All nine models included FEV_1% predicted. In all models except the Markov model of Asukai, disease progression was specified by FEV_1% predicted. All models used FEV_1% predicted to specify exacerbation frequency, mortality, utilities, and maintenance costs. In all nine models, 1-year mortality and costs were lower for a patient with moderate COPD (FEV_1% predicted about 65%) than for a patient with severe COPD (FEV_1% predicted about 40%), while the number of QALYs was higher in all models (Table 4). Five models also specified utilities during exacerbations by FEV_1% predicted (Briggs, Borg, Dal Negro, Hansen, and Wacker). Exacerbation costs were specified by FEV_1% predicted by four models (Briggs, Dal Negro, Hansen, and Wacker) (Table 3).

Validation of the model results with respect to FEV_1% predicted against the outcomes of the 3-year TORCH study showed that in three models (Borg, Briggs, and Wacker) the exacerbation rate in patients with severe COPD was significantly higher than in patients with moderate COPD (Fig. 4A), which was in line with the trial results. In the TORCH trial, mortality in patients with severe COPD was higher than in patients with moderate COPD (RR = 1.33; 95% CI 1.09–1.63). Four models reported a higher mortality rate in patients with severe COPD (Borg, Hansen, Hoogendoorn, and Wacker).

Discussion

By comparing patient heterogeneity in currently available COPD cost-effectiveness models, this study aimed to assess how

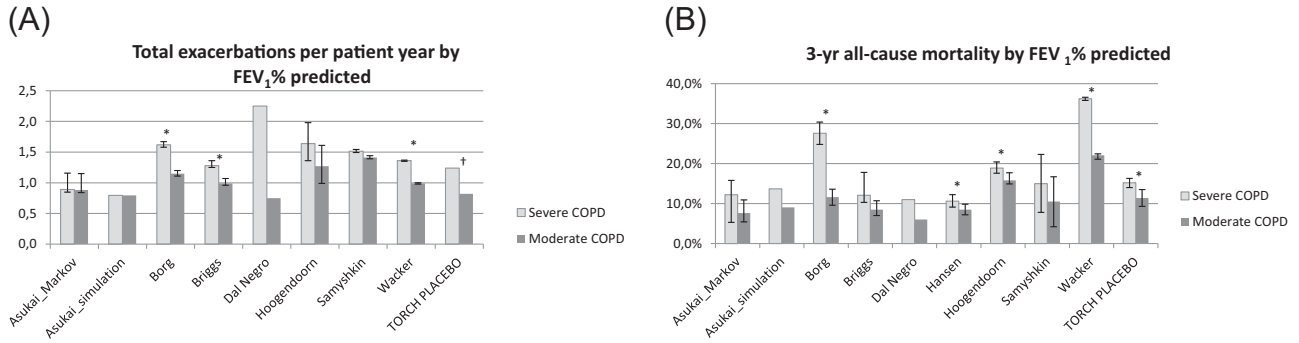

Fig. 4 – Comparison of model results for the subgroup FEV_1% predicted with empirical results of the 3-year TORCH trial for (A) exacerbations and (B) all-cause mortality. *Difference between moderate and severe COPD is statistically significant. †Difference is most likely statistically significant, but standard errors were missing. Difference in the simulation model of Asukai and the model of Dal Negro could not be tested because no uncertainty was available around the estimates. COPD, chronic obstructive pulmonary disease; TORCH, TOwards a Revolution in COPD Health.

suitable current models are to evaluate the cost-effectiveness of personalized treatment options for COPD. The patient characteristics that almost all nine models included were sex, age, smoking status, and FEV_1% predicted.

Results with respect to sex showed that the empirical data supported a difference in exacerbations between female and male patients. Several studies in the literature confirm that female patients have a higher exacerbation rate than do male patients [28–31]. Only one of the current COPD models included this relationship. Two models reported a significantly higher mortality rate in male patients, which was also found in the UPLIFT trial. However, it should be noted that in the trial female patients were on average 3 years younger and had a slightly higher FEV_1% predicted, but they were also more likely to smoke. The difference in mortality is less clear from the literature. Some studies reported lower mortality rates for women [32–34], whereas others found no difference [35–38]. Only two models specified quality of life by sex, whereas several studies found a lower quality of life for female patients [39–41].

All models included a strong association between age and mortality, which was in line with studies found in the literature [32,33,35–38]. Validation against trial results also showed a difference in mortality between young and old patients for the trial as well as most models. Most models did not specify quality of life by age, whereas several studies have shown that older patients with COPD have a lower quality of life [39,42]. Three models specified COPD-related costs by age. Several studies investigated the association between age and COPD-related costs and found no significant impact of age on costs [43–46]. This may be because age and FEV_1% predicted are correlated and in three of these studies FEV_1% was also included in the multivariate model and found to be a significant predictor.

The impact of smoking on disease progression was included in six of the models. Smokers were modeled to have a higher disease progression compared with ex-smokers, which was in line with the literature [47–49]. Three models included a higher all-cause mortality rate for smokers than for ex-smokers in their input data (Table 4). No difference in mortality rate between smokers and ex-smokers was found in the UPLIFT trial. Validation of model outcomes against trial results showed that three models reported a higher mortality rate for ex-smokers. This was probably because ex-smokers in the trial were on average 5 years older than smokers and had a lower FEV_1% predicted. Of 17 studies on predictors of mortality found in the literature, 4 studies found a higher mortality rate for smokers, 6 studies found no association, and 10 studies did not investigate this association.

With respect to FEV_1% predicted, the models are in line with the empirical data and the literature. All models include an association between FEV_1% predicted and exacerbation frequency, quality of life, mortality, and costs. In some models, the differences in exacerbations and mortality are however very small and not significant due to the large uncertainty around the estimates. The literature also showed that disease progression in terms of lung function decline seems to decrease when the FEV_1 decreases [47,48,50]. This association was not included in all models, because five of the models used the Lung Health Study as (one of the) data source (s) for disease progression, which is a study in patients with mild-to-moderate COPD showing the opposite relation (decline increases when FEV_1 decreases) [49]. It is not surprising that the model performance with respect to patient heterogeneity was best for FEV_1% predicted, because in almost all models the FEV_1% predicted is the key parameter. Five of the nine models are cohort Markov models with Markov states defined according to the 2007 GOLD classification; that is, the severity of COPD was defined by the FEV_1% predicted.

Outcomes of the different models were compared with published subgroup results of two large trials: the UPLIFT and TORCH trials. Some of the COPD models were built to extrapolate the results of clinical trials (Asukai_Markov and Samyshkin) and were populated with input data from these trials, whereas other models are population models using a wide range of different data sources as input (Hoogendoorn, Hansen, and Wacker). For the latter models, comparison with trial results may therefore be less valid because it is well known that patients included in clinical trials are a subgroup of the total COPD population. This was, for example, shown in a study of Kruis et al. [51] that found that patients participating in large clinical trials sponsored by pharmaceutical companies are on average younger, more likely to be male, have a lower FEV_1% predicted, and tend to have more exacerbations than do patients in primary care. In the current analysis, this selection bias issue was most likely the explanation that no difference in mortality was found between smokers and ex-smokers in the UPLIFT trial. Patients who continue to smoke are probably less likely to be included in clinical studies because they progress faster to more severe stages, have more comorbidities, and are more likely to die because of other smoking-related diseases. Nevertheless, among the patients who continue to smoke despite having COPD there may be relatively more patients who are less susceptible to smoking-related diseases. The true impact of trial populations being a selective group of patients on the outcomes of this study is difficult to assess. In the present study, we mainly focused on differences in outcomes between subgroups within one model or trial and therefore the impact might be limited.

The results of this study showed that all currently available models are capable of running simulations for different age- and COPD severity classes. Most models also have the ability to run analyses separately for men and women and for smokers and ex-smokers. The validity of these subgroup analyses within the models is questionable, because important input parameters have not been specified by sex, age, or smoking status. For example, the specification of higher exacerbations for women or lower quality of life with older age is not included in most models. Most models are developed to evaluate treatment options for the total general COPD population or the average COPD trial population.

Although it is not unlikely that future treatment will be increasingly tailored to age, sex, and smoking status, treatment is more likely to be personalized on the basis of clinical parameters especially when considering ethical debates and societal preferences. Exacerbations, for example, are highly associated with the number of previous exacerbations [29–31,52]. Mortality in COPD is associated not only with age and FEV_1 but also with comorbidities, BMI, dyspnea, and several other clinical parameters [32,34,36,38,53]. BMI also seems to be associated with quality of life in COPD [39,54] and comorbidities may affect COPD-related costs [44,45,55,56]. Only the more recently developed models of Asukai (simulation) and Briggs included these types of clinical parameters and are therefore more suitable than the other models to evaluate personalized treatment. Recent reviews on phenotyping in COPD showed that currently about four phenotypes have been defined in COPD that may require a different treatment strategy: emphysema, COPD with chronic bronchitis, COPD combined with asthma, and COPD with frequent exacerbations [57–60]. Information on effectiveness and cost-effectiveness of treatment options for these subgroups is needed to guide clinical guideline development and decisions for reimbursement. Three of the nine models included information on one of the phenotypes, that is, COPD with frequent exacerbations, but none of the current models is able to evaluate treatment options for the other three phenotypes. Future models should include all clinical patient characteristics currently considered to influence disease severity, prognosis, and treatment response in COPD.

The present study had some limitations. First, not all models could perform uncertainty analysis around the results for exacerbations and all-cause mortality. Therefore, it was not always possible to determine whether predicted differences between

subgroups are important within the range of uncertainty estimated. The information in the published articles of the two clinical trials was also sometimes not sufficient to calculate whether the difference between subgroups was statistically significant or not. Results of the trials by smoking status and by COPD severity did not present SDs or standard errors around the mean exacerbation rate [24,27]. The exacerbation rates in the UPLIFT trial in smokers and ex-smokers were, however, almost equal, 0.77 versus 0.83, a difference that is most likely not significant [27]. In contrast, the difference in exacerbation rate in the TORCH trial between people with severe and moderate COPD was large, 1.24 versus 0.82, and therefore this difference seems significant given the population size [24].

A second limitation was that the starting population of the models was adjusted only with respect to sex distribution, age, smoking distribution, and FEV_1%predicted to mirror the population of either the TORCH trial or the UPLIFT trial. The most recent models include much more characteristics (e.g., BMI and comorbidities) that could have been adjusted to create model populations that were even more similar to the trial populations. However, this would have made a comparison with the other models impossible.

A third limitation of the present study was that we only assessed whether there were significant differences in outcomes between the subgroups simulated with the models and whether that result was in line with the trial results and the literature. We did not focus on the results of the models in absolute terms. However, the results of the different models showed substantial variation, especially for mortality. A more detailed external validation of model results against the outcomes of the trials for the total population will be a topic of another article.

Finally, although this study aimed to compare cost-effectiveness models, it mainly focused on the comparison of clinical outcomes, not on costs. Only Table 4 presents information on costs. Validation of costs was not possible because the trials did not present costs specified by subgroups. Clinical outcomes are important outcomes for cost-effectiveness models as well because they have a high impact on quality of life and costs.

In conclusion, this study showed that most currently available COPD cost-effectiveness models include the relevant patient characteristics sex, age, smoking status, and FEV_1% predicted and are therefore able to evaluate the cost-effectiveness of personalized treatment based on these parameters. Most models, however, do not include all important associations between these characteristics and input parameters. Furthermore, treatment in COPD is more likely to be personalized on the basis of clinical parameters. Two models also included several clinical patient characteristics, such as previous exacerbations, BMI, and comorbidities, and seem to be more suitable to evaluate personalized treatment. Inclusion of other clinical parameters, such as emphysema, chronic bronchitis, and coexistence of asthma, is relevant to make the models suitable to evaluate the cost-effectiveness of treatment options for currently defined phenotypes in COPD.

Source of financial support: This study was financially supported by Boehringer Ingelheim International, GlaxoSmithKline The Netherlands, Novartis International, and Takeda Pharmaceuticals International.

REFERENCES

[1] O'Donnell JC. Personalized medicine and the role of health economics and outcomes research: issues, applications, emerging trends, and future research. Value Health 2013;16:S1–3.
[2] Redekop WK, Mladsi D. The faces of personalized medicine: a framework for understanding its meaning and scope. Value Health 2013;16:S4–9.
[3] Personalized Medicine. U.S. Food and Drug Administration. Available from: http://www.fda.gov/scienceresearch/specialtopics/personalizedmedicine/default.htm. [Accessed June 17, 2015].
[4] Hatz MH, Schremser K, Rogowski WH. Is individualized medicine more cost-effective? A systematic review. Pharmacoeconomics 2014;32:443–55.
[5] Phillips KA, Ann Sakowski J, Trosman J, et al. The economic value of personalized medicine tests: what we know and what we need to know. Genet Med 2014;16:251–7.
[6] Ramaekers BL, Joore MA, Grutters JP. How should we deal with patient heterogeneity in economic evaluation: a systematic review of national pharmacoeconomic guidelines. Value Health 2013;16:855–62.
[7] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available from: http://www.goldcopd.com. [Accessed June 17, 2015].
[8] Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182:598–604.
[9] Woodruff PG, Agusti A, Roche N, et al. Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy: making progress towards personalised management. Lancet 2015;385:1789–98.
[10] The Pharmaceutical Research and Manufacturers of America. Medicines in development for chronic obstructive pulmonary disease (COPD). 2012. Available from: http://www.phrma.org/sites/default/files/pdf/copd2012.pdf. [Accessed June17, 2015].
[11] Hoogendoorn M, Feenstra TL, Asukai Y, et al. Cost-effectiveness models for chronic obstructive pulmonary disease: cross-model comparison of hypothetical treatment scenarios. Value Health 2014;17:525–36.
[12] Price D, Gray A, Gale R, et al. Cost-utility analysis of indacaterol in Germany: a once-daily maintenance bronchodilator for patients with COPD. Respir Med 2011;105:1635–47.
[13] Borg S, Ericsson A, Wedzicha J, et al. A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. Value Health 2004;7:153–67.
[14] Hansen RN, Xu X, Sullivan SD. A dynamic cohort model of chronic obstructive pulmonary disease and its treatments. Value Health 2012;15:A54.
[15] Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, et al. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease. Value Health 2011;14:1039–47.
[16] Samyshkin Y, Kotchie RW, Mork AC, et al. Cost-effectiveness of roflumilast as an add-on treatment to long-acting bronchodilators in the treatment of COPD associated with chronic bronchitis in the United Kingdom. Eur J Health Econ 2014;15:69–82.
[17] Menn P, Leidl R, Holle R. A lifetime Markov model for the economic evaluation of chronic obstructive pulmonary disease. Pharmacoeconomics 2012;30:825–40.
[18] Asukai Y, Baldwin M, Fonseca T, et al. Improving clinical reality in chronic obstructive pulmonary disease economic modelling: development and validation of a micro-simulation approach. Pharmacoeconomics 2013;31:151–61.
[19] Briggs A, Lomas D, Rutten van-Molken M, et al. Developing a new model of COPD: from conceptualization to implementation to validation. Value Health 2013;16:A234.
[20] Risebrough NA, Briggs A, Baker TM, et al. Validating a model to predict disease progression outcomes in patients with COPD. Value Health 2014;17:A560–1.
[21] Dal Negro RW. Current annual cost calculation is the best predictor of mortality at three years in COPD. Value Health 2014;17:A590–1.
[22] Tashkin DP, Celli B, Senn S, et al. UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543–54.
[23] Calverley PM, Anderson JA, Celli B, et al. TORCH Investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775–89.
[24] Jenkins CR, Jones PW, Calverley PM, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res 2009;10:59.
[25] Tashkin D, Celli B, Kesten S, et al. Effect of tiotropium in men and women with COPD: results of the 4-year UPLIFT trial. Respir Med 2010;104:1495–504.
[26] Morice AH, Celli B, Kesten S, et al. COPD in young patients: a pre-specified analysis of the four-year trial of tiotropium (UPLIFT). Respir Med 2010;104:1659–67.
[27] Tashkin DP, Celli B, Kesten S, et al. Long-term efficacy of tiotropium in relation to smoking status in the UPLIFT trial. Eur Respir J 2010;35:287–94.
[28] McGarvey L, Lee AJ, Roberts J, et al. Characterisation of the frequent exacerbator phenotype in COPD patients in a large UK primary care population. Respir Med 2015;109:228–37.
[29] Müllerová H, Shukla A, Hawkins A, Quint J. Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. BMJ Open 2014;4:e006171.

[30] Husebø GR, Bakke PS, Aanerud M, et al. Predictors of exacerbations in chronic obstructive pulmonary disease–results from the Bergen COPD cohort study. PLoS One 2014;9:e109721.
[31] Beeh KM, Glaab T, Stowasser S, et al. Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. Respir Res 2013;14:116.
[32] Montserrat-Capdevila J, Godoy P, Marsal JR, Barbé-Illa F. Risk factors for mortality in patients with chronic obstructive pulmonary disease [in Spanish]. Aten Primaria 2015;47:498–504.
[33] Schembri S, Anderson W, Morant S, et al. A predictive model of hospitalisation and death from chronic obstructive pulmonary disease. Respir Med 2009;103:1461–7.
[34] de Torres JP, Cote CG, López MV, et al. Sex differences in mortality in patients with COPD. Eur Respir J 2009;33:528–35.
[35] Patel MS, Natanek SA, Stratakos G, et al. Vastus lateralis fiber shift is an independent predictor of mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014;190:350–2.
[36] Stolz D, Meyer A, Rakic J, et al. Mortality risk prediction in COPD by a prognostic biomarker panel. Eur Respir J 2014;44:1557–70.
[37] de Voogd JN, Wempe JB, Postema K, et al. More evidence that depressive symptoms predict mortality in COPD patients: is type D personality an alternative explanation? Ann Behav Med 2009;38:86–93.
[38] Briggs A, Spencer M, Wang H, et al. Development and validation of a prognostic index for health outcomes in chronic obstructive pulmonary disease. Arch Intern Med 2008;168:71–9.
[39] Tsiligianni I, Kocks J, Tzanakis N, et al. Factors that influence disease-specific quality of life or health status in patients with COPD: a review and meta-analysis of Pearson correlations. Prim Care Respir J 2011;20:257–68.
[40] Fishwick D, Lewis L, Darby A, et al. Determinants of health-related quality of life among residents with and without COPD in a historically industrialised area. Int Arch Occup Environ Health 2015;88:799–805.
[41] Rutten-van Mölken MP, Oostenbrink JB, Tashkin DP, et al. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? Chest 2006;130:1117–28.
[42] Punekar YS, Rodriguez-Roisin R, Sculpher M, et al. Implications of chronic obstructive pulmonary disease (COPD) on patients' health status: a western view. Respir Med 2007;101:661–9.
[43] Darnell K, Dwivedi AK, Weng Z, Panos RJ. Disproportionate utilization of healthcare resources among veterans with COPD: a retrospective analysis of factors associated with COPD healthcare cost. Cost Eff Resour Alloc 2013;11:13.
[44] Mapel DW, McMillan GP, Frost FJ, et al. Predicting the costs of managing patients with chronic obstructive pulmonary disease. Respir Med 2005;99:1325–33.
[45] Miravitlles M, Murio C, Guerrero T, Gisbert R. Costs of chronic bronchitis and COPD: a 1-year follow-up study. Chest 2003;123:784–91.
[46] Jansson SA, Andersson F, Borg S, et al. Costs of COPD in Sweden according to disease severity. Chest 2002;122:1994–2002.
[47] Vestbo J, Edwards LD, Scanlon PD, et al. ECLIPSE Investigators. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med 2011;365:1184–92.
[48] Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med 2008;178:332–8.
[49] Scanlon PD, Connett JE, Waller LA, et al. Lung Health Study Research Group. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med 2000;161:381–90.
[50] Casanova C, de Torres JP, Aguirre-Jaíme A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med 2011;184:1015–21.
[51] Kruis AL, Ställberg B, Jones RC, et al. Primary care COPD patients compared with large pharmaceutically-sponsored COPD studies: an UNLOCK validation study. PLoS One 2014;9:e90145.
[52] Make BJ, Eriksson G, Calverley PM, et al. A score to predict short-term risk of COPD exacerbations (SCOPEX). Int J Chron Obstruct Pulmon Dis 2015;10:201–9.
[53] Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1791–7.
[54] Villar Balboa I, Carrillo Muñoz R, Regí Bosque M, et al. Factors associated with the quality of life in patients with chronic obstructive pulmonary disease [in Spanish]. Aten Primaria 2014;46:179–87.
[55] Huber M, Wacker M, Vogelmeier CF, Leidl R. Excess costs of comorbidities in chronic obstructive pulmonary disease: a systematic review. PLoS One 2015;10:e0123292.
[56] Huber M, Wacker M, Vogelmeier CF, Leidl R. Comorbid influences on generic health-related quality of life in COPD: a systematic review. PLoS One 2015;10:e0132670.
[57] Miravitlles M, Soler-Cataluña JJ, Calle M, et al. Spanish guideline for COPD (GesEPOC): update 2014. Arch Bronconeumol 2014;50(Suppl. 1): 1–16.
[58] Segreti A, Stirpe E, Rogliani P, Cazzola M. Defining phenotypes in COPD: an aid to personalized healthcare. Mol Diagn Ther 2014;18:381–8.
[59] Rothe T. Phenotype specific therapy of COPD [in German]. Praxis (Bern 1994) 2014;103:1509–14.
[60] Vestbo J. COPD: definition and phenotypes. Clin Chest Med 2014;35:1–6.